Paper No. 38

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MAR TORMO, ANA M. TARI and GABRIEL LOPEZ-BERESTEIN

Appeal No. 2000-1898
Application No. 08/726,211

HEARD: November 29, 2001

Before WILLIAM F. SMITH, SCHEINER, and ADAMS, Administrative Patent Judges.

WILLIAM F. SMITH, Administrative Patent Judge.

VACATUR AND REMAND TO THE EXAMINER

After considering the record and hearing oral argument, we have concluded that this case is not in condition for a decision on appeal. For the reasons that follow we vacate the examiner's rejection under 35 U.S.C. § 103 and remand the application to the examiner for further action consistent with the views expressed herein.[1]

[1] Lest there be any confusion, when the board vacates an examiner's rejection, the rejection ceases to exist. See Ex parte Zambrano, 58 USPQ2d 1312 (Bd. Pat. App. & Int. 2001).

REPRESENTATIVE CLAIMS

At the time the Notice of Appeal was filed in this application, claims 1 through 37, 39 through 41, 44, 46, 48 through 50, 52 through 54 and 56 were pending and subject to rejection. Claims 38, 43, 45, 47 and 55 were also pending but stated to be free of rejection and only objected to as depending from a rejected claim. An amendment was submitted with the Reply Brief canceling claims 1 through 9, 31 through 37, 39 through 41, 48 through 50, 52 through 54 and 56.[2] Thus, claims 10 through 30, 44, and 46 are before us for review on this appeal and claims 38, 43, 45, 47 and 55 are pending but are free of rejection.

Claims 10, 21, 43 and 45 are representative of the subject matter pending in this application and read as follows:

10. A method of inhibiting proliferation of a Bcl-2-associated disease cell comprising obtaining a first polynucleotide that hybridizes to a second polynucleotide under intracellular conditions, mixing the first polynucleotide with a neutral lipid to form a composition comprising a polynucleotide/lipid association, and administering said association to said Bcl-2-associated disease cell to inhibit the proliferation of said disease cell, wherein said cell has a t(14;18) translocation, and wherein the second polynucleotide comprises at least 8 bases of the translation initiation site of Bcl-2 mRNA.

21. A method of inhibiting proliferation of a Bcl-2-associated disease cell having a t(14;18) translocation comprising:

(a) obtaining an oligonucleotide of from about 8 to about 50 bases and complementary to at least 8 consecutive bases of the translation initiation site of Bcl-2 mRNA;

(b) mixing the oligonucleotide with a neutral lipid to form a neutral oligonucleotide/lipid association; and

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[2] The examiner approved the amendment for entry, but to date the amendment has not been formally entered in the administrative file. On return of the application, the examiner should see to it that all papers have been properly entered in the file. In entering the amendment, the examiner stated in a communication mailed July 27, 2000 (Paper No. 32), that a rejection under 35 U.S.C. § 103(a) "over Evan or Reed or Green et al. each in view of Tari et al. is withdrawn in view of the cancellation of the claims."

(c) administering said association to said Bcl-2-associated disease cell to inhibit the proliferation of said disease cell.

43. The method of claim 10, wherein said first polynucleotide is a P-ethoxy oligonucleotide.

45. The method of claim 21, wherein said first oligonucleotide is a P-ethoxy oligonucleotide.

BACKGROUND

The claims remaining under rejection in the application are directed to a method of inhibiting proliferation of a Bcl-2-associated disease cell. As explained by appellants:

> bcl-2 is an oncogene with tumorigenic potential due to its capacity to block programmed cell death. The present invention employs liposomal antisense oligodeoxynucleotides to inhibit the production of Bcl-2 so that tumor cells can regain the capacity to enter programmed cell death. The present invention may also be used to treat hematologic malignancies, both leukemias and lymphomas, including follicular and nonfollicular lymphomas, chronic lymphocytic leukemia, and plasma cell dyscrasias; solid tumors like those associated with breast, prostate and colon cancer; and immune disorders, which are associated with Bcl-2 expression.

Specification, page 9, line 20 - page 10, line 2. A broader description of the invention is also set forth by appellants as follows:

> In another embodiment, the polynucleotide is associated with a lipid. A polynucleotide associated with a lipid may be encapsulated in the aqueous interior of a liposome, interspersed within the lipid bilayer of a liposome, attached to a liposome via a linking molecule that is associated with both the liposome and the polynucleotide, complexed with a lipid, dispersed in a solution containing a lipid, mixed with a lipid, combined with a lipid, contained as a suspension in lipid, contained or complexed with a micelle, or otherwise associated with a lipid.

Specification, page 4, lines 20-27. Lipids used in this invention are defined by appellants as follows:

> The term "lipids" as used in this specification and the claims denotes any form of both naturally occurring and synthetic lipids or liposomes. They are fatty substances and are well-known by those of skill in the art. The lipids of the

> present invention are not limited to any particular structure in solution. For example, they may be present in a bilayer structure, as micelles, or with a "collapsed" structure. They may also simply be interspersed in a solution, possibly forming aggregates which are not uniform in either size or shape. The lipid may advantageously be comprised of the lipid dioleoylphosphatidylcholine, however other lipids such as other phosphatidylcholines, phosphatidylglycerols, and phosphatidylethanolamines may also be employed.

Specification, page 5, lines 1-9.

As seen from the claims reproduced above, the claimed invention requires the administration of a "polynucleotide/lipid association." Appellants discuss this "association" as follows:

> In a preferred embodiment of the invention, the antisense oligo- or polynucleotides and expression vectors may be associated with a lipid. A polynucleotide associated with a lipid may be encapsulated in the aqueous interior of a liposome, interspersed within the lipid bilayer of a liposome, attached to a liposome via a linking molecule that is associated with both the liposome and the polynucleotide, entrapped in a liposome, complexed with a liposome, dispersed in a solution containing a lipid, mixed with a lipid, combined with a lipid, contained as a suspension in a lipid, contained or complexed with a micelle, or otherwise associated with a lipid. The lipid or lipid/oligonucleotide associated compositions of the present invention are not limited to any particular structure in solution. For example, they may be present in a bilayer structure, as micelles, or with a "collapsed" structure. They may also simply be interspersed in a solution, possibly forming aggregates which are not uniform in either size or shape.

Specification, page 21, lines 13-25. Lipids are also defined by appellants as "fatty substances which may be naturally occurring or synthetic lipids. For example, lipids includes the fatty droplets that naturally occur in the cytoplasm as well as the class of compounds which are well known to those of skill in the art which contain long-chain aliphatic hydrocarbons and their derivatives, such as fatty acids, alcohols, amines, amino alcohols, and aldehydes." Specification, page 21, line 26-page 22, line 4. As seen, one specific type of "polynucleotide/lipid association" within the scope of the present invention is a liposome which is discussed on pages 22-25 of the specification.

Of interest is the disclosure concerning phospholipids useful for preparing the liposomes of the present invention appearing in the specification at page 5, lines 4-15 as follows:

> For example, they may be present in a bilayer structure, as micelles, or with a "collapsed" structure. They may also simply be interspersed in a solution, possibly forming aggregates which are not uniform in either size or shape. The lipid may advantageously be comprised of the lipid dioleoylphosphatidylcholine, however other lipids such as other phosphatidylcholines, phosphatidylglycerols, and phosphatidylethanolamines may also be employed.
>
> In yet another embodiment, there is provided a composition comprising a polynucleotide that hybridizes to a Bcl-2-encoding polynucleotide.
>
> In still yet another embodiment, there is provided a composition comprising an expression construct that encodes a polynucleotide that hybridizes to a Bcl-2-encoding polynucleotide, wherein said first polynucleotide is under the control of a promoter that is active in eukaryotic cells.

Examples 1-3 of the specification describe results obtained from in vitro experiments using liposomal oligonucleotides. Nuclease-resistant p-ethoxy-oligonucleotides were prepared and formulated into a liposomal preparation. See Examples 1 and 2 of the specification. As explained in Example 2, the oligonucleotides were added to "phospholipids." It does not appear that the specification describes the phospholipids used in the examples in any detail apart from they were apparently purchased from Avanti Polar Lipids in Alabaster, Alabama. Example 3 is stated to show oligonucleotide inhibition of Bcl-2 protein expression. Examples 4-6 of the specification are directed to "In Vivo Testing", "Clinical Trials" and "Human Treatment and Clinical Protocols" respectively. However, it appears that these examples are prophetic in nature and do not represent work which has actually been preformed.

It is our understanding that claims 10 through 30, 44 and 46 stand rejected under 35 U.S.C. § 103(a) with the examiner relying upon references identified as Abubakr[3], Pocock[4], Cotter[5], Tari[6] and Evan[7] relied upon as evidence of obviousness. See the Examiner's Answer, page 4, last full paragraph. However, the Examiner's Answer does not contain a statement of a rejection. Rather, the Answer, after stating the then pending rejections, proceeds to a discussion of appellants' arguments in this appeal. The examiner does not refer us to any particular paper for an explanation as to why any claim is unpatentable on the basis of these references.

This is problematic since there have been at least five rejections entered in this application file, two of which were final rejections. The last final rejection was entered July 16, 1999 (Paper No. 21). In relevant part, the examiner states at page 9 thereof the rejection based on Abubakr, Pocock, Cotter, Tari and Evan is "maintained for the reasons of record in the previous Office action." However, the examiner went on and apparently summarized the rejection. Reviewing the previous Office action (Paper No. 18), entered January 4, 1999, we find that claims are rejected on the basis of Abubakr, Pocock, Cotter and Tari, but not Evan, while two claims, claims 4 and 32, are rejected on the basis of Abubakr, Pocock, Cotter, Tari and Evan. Suffice it to say the record lacks a clear, concise and coherent statement why the claims remaining in this

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[3] Abubakr et al. (Abubakr), "Effectiveness of Bcl-2 antisense oligodeoxynucleotides (AS-ODN) against human follicular small-cleaved cell lymphoma (FSCCL)-SCID mice xenograft model." Blood, Vol. 82, No. 10, Suppl 1, page 374 A (Dec. 1993)
[4] Pocock et al. (Pocock), "In vivo suppression of B-cell lymphoma with Bcl-2 antisense oligonucleotides." Blood, Vol. 82, No. 10, Suppl 1, page 200A (Dec. 1993)
[5] Cotter et al. (Cotter), "Antisense oligonucleotides suppress B-cell lymphoma growth in a SCID-hu mouse model." Oncogene, Vol. 9, pages 3049-55 (Oct. 1994)
[6] Tari et al. (Tari) 5,417,978 May 23, 1995
[7] Evan WO 93/20200 Oct. 14, 1993

application are considered to be unpatentable on the basis of Abubakr, Pocock, Cotter, Tari and Evan.

In responding to the examiner's rejections under 35 U.S.C. § 103(a), appellants rely upon a declaration of co-appellants Lopez-Berestein and Tari filed under 37 CFR § 1.132, executed June 10, 1998. The declaration sets forth the results obtained from experiments designed to examine the effects of lipid charge on antisense delivery. To this end, the study used negatively-charged oligonuceotide/lipid associations, positively-charged oligonucleotide/lipid associations and oligonucleotide/lipid associations which contained a neutral lipid. The results are discussed in paragraphs 6 and 7 of the declaration as follows:

> 6. These results are surprising and unexpected as this indicates that only the neutral DOPC lipids and not charged lipids can be used to safely and effectively deliver antisense oligonucleotides to cells and thereby achieve selective cytotoxicity and cell growth inhibition.
> 7. In view of the above-described studies and those disclosed in the specification, it is clear that the methods and compositions employing antisense BCL-2 in association with neutral lipids disclosed and claimed in this application have surprising and unexpected properties with respect to similar methods and compositions employing antisense BCL-2 lipid associations wherein the lipid association has an overall positive or negative charge.

The examiner's response to the declaration as expressed in the Examiner's Answer is as follows:

> The results disclosed in the declaration are not commensurate in scope with appellants' alleged unexpected result that neutral lipids are less toxic that charged lipids. The experiments disclosed in the declaration used only one neutral lipid (DOPC) and two charged lipids (DMPG and DC-CHOL). Furthermore, the lipids were only tested at one ratio of neutral to charged lipids (70:30). Therefore, appellants do not have sufficient support to show that all neutral lipids are less toxic that all charged lipids. Additionally, Tari et al. discloses that liposomes composed of DOPC are not toxic to cells (column 1, lines 14-16). Thus, there is no surprise in the fact that DOPC is non-toxic.

Examiner's Answer, page 7.

In reviewing the record, we find that appellants filed a declaration of co-appellants Lopez-Berestein and Tari under 37 CFR § 1.131 in response to the examiner's first Office action. The Rule 131 declaration acknowledges there is a third inventor listed for this application, Mar Tormo. See the first paragraph of the Rule 131 declaration ("we, along with Dr. Mar Tormo, are co-inventors of the subject matter of the captioned patent application USSN 08/726,211."). However, Dr. Tormo did not execute the declaration.

Furthermore, we have discovered U.S. Patent No. 5,855, 911 issued January 5, 1999 ('911 patent), which lists co-appellants Lopez-Berestein and Tari as inventors. Based on the August 29, 1995 filing date of the '911 patent and the differing inventive entities of the '911 patent and this application, the '911 patent appears to be available as prior art under 35 U.S.C. § 102(e).

To the extent we understand the examiner's position on the remaining rejection under 35 U.S.C. § 103(a), Evan is relied upon only for its disclosure of certain antisense oligonucleotides which are purportedly the same as certain of the oligonucleotides required by dependent claims pending in this application. However, a reading of Evan in its entirety reveals that the reference contains more relevant disclosure.

Evan is directed to administering Bcl-2 antisense oligonucleotides. See the abstract. At page 15, lines 1-6 Evan states:

> If desired, the antisense oligonucleotide can be conjugated with hydrophobic derivatives as taught in FR 2 649 321 to protect it from nucleases and to improve transport across cell membranes. The hydrophobic moiety may be cholesterol as taught by Zon in "Oligodeoxynucleotides: Antisense Inhibitors of Gene Expression", pp 234-247, J.S. Cohen (Ed), CRC Press, Boca Raton, FL, 1989.

The examiner does not appear to have considered the referenced French patent or the Zon reference. At page 59 of Evan, delivery of the antisense oligonucleotides is discussed as follows:

> Effective delivery of bcl-2 antisense oligonucleotides in vivo is via liposomes (Loke et al, 1988; 1989). These are targeted in a variety of ways. For example, by coating the liposomes with antibodies specific for the tumour cells. The significant advantage of anti-bcl-2 strategies is that inhibiting bcl-2 is not especially likely to be toxic to bystanding cells even if it enters them. This is because most normal cells are prevented from undergoing apoptosis by a variety of cytokine mechanisms. It is specifically the tumour cell that needs to avoid apoptosis in order to survive and grow and thereby is dependent upon continuous bcl-2 expression.

A discussion of this portion of Evan occurred during oral argument. Counsel was informed that the referenced Loke 1988 and 1989 documents could not be found in this record. Counsel kindly forwarded copies of the two Loke documents by facsimile transmission on December 3, 2001, stating:[8]

> Appellants have argued in this appeal that the references relied upon by Evan teach only charged and not neutral liposomes (see, e.g., Reply Brief at top of page 6). Appellants have reviewed the Loke et al. references and find that the Loke et al., 1988, article describes the preparation of liposomes composed of phosphatidyl serine at the top of page 284. No mention of liposomes or lipid complexes can be found in the Loke et al, 1989, article. The fact that phosphatidly serine is a charged, and not a neutral, lipid can be seen from the enclosed structure and description of phosphatidyl serine, recently obtained off the internet, showing it to be an acidic, anionic, phospholipid.

To date, it does not appear from the record that the examiner has considered the Loke documents, especially in light of counsel's comments.

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[8] The merits panel thanks counsel for his cooperation in this matter.

VACATUR

We begin with the proposition that this board serves a board of review, not as a de novo examination tribunal. 35 U.S.C. § 6b ("the [board] shall, on written appeal of an applicant, review adverse decisions of examiners upon applications for patents ...."). Findings of fact and conclusion of law by the USPTO must be made in accordance with the Administrative Procedure Act, 5 U.S.C. § 706(A),(E), 1994. Dickinson v. Zurko, 527 US 150, 158, 119 S: Ct. 1816, 1821, 50 USPQ2d 1930, 1934 (1999). Our reviewing court has held that findings of fact must be supported by substantial evidence within the record. In re Gartside, 203 F.3d 1305, 1315, 53 USPQ2d 1769, 1775 (Fed. Cir. 2000) ("because our review of the board's decision is confined to the factual record compiled by the board ... the 'substantial evidence' standard is appropriate for our review of board fact findings, see 5 U.S.C. § 706(2)(E).") See also In re Lee, 277 F.3d 1338, 61 USPQ2d 1430 (Fed. Cir. 2002) (board decision denying patent must be founded on necessary findings and must provide an administrative record showing the evidence which the findings are based; the board must assure the requisite findings are made, based on evidence of record). What the Federal Circuit rightfully expects from the board, the board expects from the examiner.

The record forwarded to the board is not susceptible to meaningful review. For example, we have an Examiner's Answer that does not contain a statement of the rejection. In essence the examiner would have us perform a paper chase through the record to determine his position. We decline to do so.

Further, it does not appear that the examiner has considered the applied references in their entirety and as a consequence, relevant disclosures have not been

discussed on the record by the examiner. Nor does it appear that the examiner has considered the proffered evidence of nonobviousness, the Rule 132 declaration, using appropriate legal standards. Also, it appears that the examiner has accepted the Rule 131 declaration when, on its face, it is not in compliance with the rule, i.e., it is signed by less than all of the named inventors. Finally, the '911 patent is relevant prior art which has not been discussed on this record by either the examiner or appellants.

We do not vacate an examiner's rejection and remand the application to the examiner for further consideration lightly. We understand the application has been pending for an extended period of time and has been subject to five different Office actions culminating in this appeal proceeding. However, a record forwarded to this board in connection with an ex parte appeal must be susceptible to meaningful review. This did not happen here. Under these circumstances, we find it appropriate to vacate the examiner's rejection and remand the application to the examiner to take further action consistent with the following views.

REMAND

1. Obviousness

Upon return of the application, the examiner should take a step back and reassess the patentability of the claims on appeal under this section of the statute. In so doing, the examiner should take into account all relevant prior art and appropriate legal standards. If the examiner believes that the claims on appeal are unpatentable under this section of the statute, we urge the examiner to express any further rejection using the model set forth at MPEP § 706.02(j). Adherence to this model will of necessity result in the examiner performing the necessary fact-finding in support of the legal

conclusion of obviousness and consider the claims in the individual manner. In performing this reassessment, the examiner should take into account the following items.

2. Tari, '911 patent and Evan

Tari and Evan appear to be the most relevant prior art relied upon by the examiner. In addition, the '911 patent appears to be relevant in determining the patentability of the claims on appeal. As indicated above, Evan specifically teaches that antisense Bcl-2 oligonucleotides can be conjugated to a hydrophobic derivative to protect the oligonucleotide from nucleases and improve their transport across cell membranes. Evan, page 15. However, since the examiner has not considered the French patent document and Zon publication cited in support of this teaching in Evan, this disclosure cannot be put in a proper factual context. As also indicated above, Evan specifically describes Bcl-2 antisense oligonucleotides delivered in vivo by way of liposomes. Again, the examiner has not explicitly considered the Loke 1988 and 1989 documents referenced in this portion of Evan on the record.

As part of the examiner's reassessment of the patentability of the claims on appeal, he should consider the Loke documents. Furthermore, he should obtain and review an English language translation of the French patent document as well as obtain and review the Zon publication referenced on page 15 of Evan. While counsel states the Loke documents describe non-neutral lipids are used in forming those liposomes, we note that Evan states at page 15 that cholesterol can be used as a hydrophobic moiety as taught by Zon. Assuming arguendo the examiner confirms appellants' position that the Loke documents are concerned with non-neutral lipids, it may be that the French

patent document or Zon would provide other relevant evidence in regard to the use of neutral lipids to protect Bcl-2 antisense oligonucleotides from nucleases and to improve their transport across cell membranes.

In this regard, the examiner should initially focus his attention on the independent claims which merely require a "polynucleotide/lipid association" wherein the lipid is a neutral lipid. It may be that an Bcl-2 antisense oligonucleotide conjugated with cholesterol as specifically taught on page 15 of Evan would be considered a polynucleotide/lipid association based upon a neutral lipid as required by the claims remaining in this application. In this regard, we again note that the present specification states at page 23 that cholesterol is a lipid useful in the present invention.

Tari identifies two concerns in using antisense oligonucleotides to inhibit gene expression: (1) cellular instability and (2) cellular uptake. Tari, column 1, lines 40-63. Tari indicates that the first problem, cellular instability, can be addressed through use of modified phosphodiester analogs such as phosphorothioates and methyl phosphonates. Id. Tari's invention is directed to liposomal methyl phosphonate oligonucleotide compositions comprising at least one phospholipid and an antisense methyl phosphonate oligonucleotide which is entrapped in the liposome. Tari column 1, line 66-column 2, line 5. As stated by Tari:

> The advantages of the invention include improved stability of the antisense oligonucleotides compositions under biologic conditions, improved uptake of the composition in cells, improved incorporation efficiency of the oligonucleotides into liposomes, and enhanced specific therapeutic effect of the antisense oligonucleotides against CML and other disease conditions in which similar gene rearrangements are observed.

Tari, column 2, lines 49-56.

Tari prefers the use of the neutral lipid phosphatidylcholine because both phosphatidylcholine and methyl phosphonate oligonucleotides are neutral molecules and on that basis should be compatible and that phosphatidylcholine is a "well-studied lipid and is easy to handle." Tari, column 5, lines 18-29. In Table 4, Tari provides data related to the incorporation efficiency of liposomes based upon various lipids including neutral and non-neutral lipids. While the non-neutral lipid (dioleoyl phosphatidylserine) had a relatively high incorporation efficiency, Tari states that the neutral lipid dioleyl phosphatidylcholine was the easiest to handle. Finally, Tari reports that empty liposomes based upon the neutral lipid dioleyl phosphatidylcholine did not inhibit growth of the tested cell. See, e.g., Tari, column 7, lines 15-17.

The '911 patent is similar to the disclosure in Tari but differs in two important ways. First the liposomes described in the '911 patent for delivering antisense oligonucleotides must be substantially free of anionic and cationic phospholipids and cholesterol, i.e., the phospholipids must be neutral. '911 patent, column 3, lines 23-30. See also claim 1 of the '911 patent (liposomal composition of antisense oligonucleotides including (a) a liposomal which consists essentially of neutral phospholipids ....") Of equal importance is the disclosure in the '911 patent that the antisense oligonucleotides described therein may be p-ethoxy oligonucleotides. In Example 2, the '911 patent states that p-ethoxy oligos were purchase from Oligos Therapeutics in Willsonville, Oregon. Since the '911 patent was filed on August 29, 1995, and this application was filed on October 4, 1996, the '911 patent provides evidence that applicants in this application were not the first to use p-ethoxy oligonucleotide antisense molecules. This

raises a question as to the propriety of the examiner withdrawing the rejection of the claims directed to this embodiment.

3. Rule 132 Declaration

To the extent the disclosures of Evan, Tari and the '911 patent establish a prima facie case of obviousness, that does not end the matter as appellants rely on the Rule 132 declaration as evidence of nonobviousness. Without a clear and definite explanation of the prima facie case from the examiner, it is difficult to evaluate the declaration to determine what weight, if any, should be given in the obviousness determination. For example, evidence of nonobviousness based upon comparative testing must represent a comparison with the closest prior art. In re Boesch, 617 F.2d 272, 276, 205 USPQ 215, 219 (CCPA 1980). Viewing Evan on one hand and Tari and the '911 patent on the other, it may be that two different comparisons need to be made on the facts of this case. The proffered comparison would be premised upon Evan being the closest prior as describing an polynucleotide/lipid association Bcl-2 antisense oligonucleotide. Assuming arguendo that the cholesterol lipid conjugate described at page 15 of Evan is not a polynucleotide/lipid association based upon a neutral lipid as required by the claims on appeal, the question becomes why would it have been obvious to one of ordinary skill in the art to select a neutral lipid in Evan? The Rule 132 declaration provides evidence, limited as it may be that the neutral lipid tested therein provided results which are different from those obtained from using cationic and anionic lipids. That evidence may be a sufficient rebuttal of a prima facie of obviousness based upon Evan as the principal evidentiary document.

However, viewing Tari and the'911 patent as the closest prior art, a prima facie case may be constructed on the basis that it would have been obvious to one of ordinary skill in the art to use as the antisense oligonucleotide in the inventions of those disclosures, a Bcl-2 antisense oligonucleotide as described in Evan. On the basis of this rejection, the proffered comparison would be entitled to less weight. The '911 patent describes the claimed method including use of a neutral lipid in the polynucleotide/lipid association but for the antisense oligonucleotide being a Bcl-2 oligonucleotide. Viewed in this light, the proper comparison would be a comparison of various polynucleotide/lipid associations, each based upon a neutral lipid, differing only in the antisense oligonucleotide contained therein. We do not have such evidence of record.

Furthermore, in considering evidence of unexpected results, it has been held that "the basic property of utility must be disclosed in order for affidavit evidence of unexpected properties to be offered." In re Davies, 475 F.2d 667, 670, 17 USPQ 381, 385 (CCPA 1973). It does not appear that the specification of this application describes the unexpected results which are now urged, i.e., neutral lipids are better than lipids that contain a positive or negative charge. If anything, a reading of the specification as a whole leaves one to believe that each of the three types of lipids would work equally well.

4. Rule 131 Declaration

Upon return of the application, the examiner should take a step back and review the references which were withdrawn in view of appellants' presentation of the Rule 131 declaration. As noted above, the declaration was signed by only two of the three

inventors named in this application and as such does not comply with the rule. Absent a proper Rule 131 declaration, it appears that the rejection should be reinstated.

FUTURE PROCEEDINGS

We state that we are not authorizing a Supplemental Examiner's Answer under 37 CFR § 1.193(b)(1).

VACATED; REMANDED

William F. Smith
Administrative Patent Judge

Toni R. Scheiner
Administrative Patent Judge

Donald E. Adams
Administrative Patent Judge

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